IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of
Mamoru OHASHI et al
Serial No : 09/529,715
Filed : April 19, 2000
For : FAST-DISSOLVING PHARMACEUTICAL COMPOSITION

Group Art Unit:1616
Examiner : Sharmila Gollamudi

DECLARATION (D)

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

I, Mamoru OHASHI, a citizen of Japan residing at 10-23-501, Ogaki 6-chome, Ritto-shi, Shiga-ken, Japan, declare as follows.

1. I was graduated from Kyoto Pharmaceutical University in March 1988, and completed the master's course at the same university in March 1990.

Since April 1990 up till the present, I have been an employee of Dainippon Pharmaceutical Co., Ltd. and had been engaged in researches and developments of drug product formulation, particularly in solid dosage form in Pharmaceutical Research Laboratory of said company.

2. I am one of the co-inventors for the invention described in U.S Serial No. 09/529,715 and am familiar with the subject matter thereof.

3. I have read the cited Negoro el al., U.S. patent 5,258,382, Muller et al. U.S. Patent 5,858,410, Arbuthnot et al., U.S Patent 6,458,811 and Shneider et al., U.S. Patent 5,356,636 and am familiar with the subject matter thereof.

4. Under my supervision, the following experiment has been done for the purpose of showing that the AS-3201 particles have variable particle size in each pulverization trial by Jet Mill, and further showing the manufacturing

method of the tablets which have been subjected to the clinical studies in the U.S.A., as well as the dissolution properties of the tablets subjected to the clinical studies.

AS-3201 means (R)-2-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydropyrrolo-[1,2-a]pyrazine-4-spiro-3'-pyrrolidine-1,2',3,5'-tetrone.

Experiment 1: Pulverization of AS-3201 crystals with Jet Mill

AS-3201 crystals prepared in a similar manner as disclosed in Example 1 of Negoro et al., U.S. Patent 5,258,382 were micronized using Single Truck Jet Mill (manufactured by SEISHIN ENTERPRISE Co., Ltd.) with compression air pressure of 6 - 7 kgf/cm^2 to give powders. The mean particle size of the powders was measured by the following method.

Method for measuring the particle size:

The mean particle size was measured using a laser diffraction particle size distribution analyzer [HELOS (trademark), manufactured by SYMPATEC GmbH, Germany] with a RODOS dry-air dispersing modules at 0.5 bars in dispersion air pressure, and calculated from cumulative particle distribution on volume basis.

The results are shown in Table 1.

Table 1 Mean particle size of AS-3201 pulverized by Jet Mill

Symbol	Lot number	Mean particle size (μm)
(A)	T99001, Batch #1	1.37
(B)	T99001, Batch #2	1.18
(C)	T03001	1.57
(D)	T03005	1.37
(E)	T03006	1.25
(F)	T03007	1.19
(G)	R94005	1.62

Note 1: Symbols (A) to (F): AS-3201 particles contained in the tablets which have been subjected to clinical studies in the U.S.A.

2: Symbol (G): AS-3201 particles contained in the tablets which have been subjected to clinical study in Japan.

As is seen from the data shown in Table 1, when AS-3201 particles were pulverized by Jet Mill, the particles had mean particle size of 1.36 μm

(in average), 1.18 μm (at minimum), and 1.62 μm (at maximum).

Expepriment 2: Preparation of tablets which have been subjected to clinical studies in the U.S.A. and dissolution rate of the AS-3201 therefrom

(1) Preparation of tablets

By using the microparticles (1.18 μm) of AS-3201 of Symbol (B) in the above Table 1, tablets were prepared with the formulation as shown in Table 2 by the following method.

The micronized AS-3201 powders (Lot. T99001, Batch#2) obtained in Experiment 1, lactose and low substituted hydroxypropylcellulose (hereinafter, abbreviated as "L-HPC") were charged into a fluid bed granulator and drier, and then the mixture was granulated by spraying thereto a solution of tartaric acid in a 5% aqueous hydroxypropylcellulose (hereinafter, abbreviated as "HPC") solution. The granules were dried, and thereto was added magnesium stearate, and the mixture was blended in a V-blender. The resultant was compressed on a rotary tableting machine to give tablets.

Table 2 Formulation of tablets of AS-3201 which have been subjected to clinical studies in the U.S.A.

Formulation	Amount	Content per each tablet
AS-3201	1,000 g	10 mg
Lactose	8,400 g	84 mg
L-HPC	2,500 g	25 mg
HPC	250 g	2.5mg
Tartaric acid	100 g	1 mg
(Purified water)	(4,750 g)	———
Mg stearate	250 g	2.5 mg
Totally	12,500 g	125 mg

(2) Dissolution test of the tablets

The dissolution of the AS-3201 from the tablets obtained in Experiment 2 (1) was evaluated under the same condition disclosed in U.S. Patent Application Serial No. 09/529,715. Two 10 mg tablets, corresponding

to 20 mg of AS-3201 were tested according to Paddle method (50 rpm) specified in the Fourteenth Edition of the Pharmacopoeia of Japan, using a 0.2 M phosphate buffer (pH 6.5, 900ml) as a test solution. The quantitative assay of AS-3201 was carried out by spectrophotometry at 300 nm. The results are shown in Table 3.

Table 3 Dissolution rate of AS-3201 from tablets which have been subjected to clinical study in the U.S.A.

	Dissolution rate (%)			
	After 5 min.	After 10 min.	After 15 min.	After 30 min.
Tablets in Experiment 2(1) (1.18 μm)	66.6	89.2	95.3	100.0

As is seen from the above Table 3, the tablets used in the clinical study in the U.S.A. had excellent dissolution rate.

5. Conclusion

(1) AS-3201 particles pulverized by Jet Mill had mean particle size of 1.36 μm (in average), 1.18 μm (at minimum), and 1.62 μm (at maximum).

(2) The tablets used in the clinical study in the U.S.A. (mean particle size of AS-3201: 1.18μm) had excellent dissolution rate.

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United Stated Code, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 19 day of May, 2005

Mamoru Ohashi

Mamoru Ohashi